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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
KAUFMAN,C	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/021,660	Applicant(s) BARON ET AL.	
	Examiner Claire M. Kaufman	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2000* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *57-81* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *57-81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

The request filed on December 6, 2000 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/021,660 is acceptable and a CPA has been established. An action on the CPA follows.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

The amendment filed 3/3/00 remains objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The deletion of the definition of "Synergistic effect" on page 11 of the specification presents new matter. The reasons for this is that the original definition in the specification is consistent with but more limiting than the meaning as the term is generally used in the art. Applicants are allowed to narrow the meaning of terms in the application, but once done, the meaning cannot then be expanded.

Applicant is required to add back what was deleted in the reply to this Office Action.

The specification remains objected to because:

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Objections

Claims 60 and 61 remain objected to because of the following informalities: "bone morphogenetic protein" is incorrect. The second word should be "morphogenic" (see *e.g.*, page 18, line 24 of specification). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 57, 61, 62, 76-79, 81 and dependent claims 58-60, 63-75 and 80 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention as set forth in the previous Office action (paper #14, pages 3-4) and as repeated below.

Claim 57 is indefinite because it is unclear what is encompassed by a WNT compound. There is no definition in the specification, and the prior art has not set forth a limited definition of such a compound. The claim is also indefinite because it is unclear what the second compound *comprises* beside TGF-ß. That information is important because without it, it is unclear if the TGF-ß is the active ingredient of the second compound.

Claim 57 recites the limitation "one or more compounds " in line 6. There are only two compounds listed in the claim. There is insufficient antecedent basis for this limitation in the claim. There is, however, antecedent basis for a first and second compound, so that the claim could read instead "said first and optionally said second compound". It appears from the claim that the first compound must be present.

Claim 61 recites the limitation "the bone morphogenetic protein" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 57 does not recite that type of protein, however, claim 60 does.

Claim 62 is indefinite because it is unclear where in the step of claim 57 the further step of the instant claim occurs.

Claim 76 is indefinite because it is unclear what the relationship between steps (a) and (b) are. It is unclear if the contacting leads to the stimulation or if it is an independent unrelated step.

Claim 77 is indefinite because it is unclear where in step (a), the selection is to occur. Additionally, the claim is indefinite because it is unclear how to select the compound, and if the compound is cDNA and/or the protein expressed from a cDNA.

Claim 78 is indefinite because the relationship between the selecting and screening is unclear. That is, it is unclear if one selects a compound and then screens the library of compounds.

Claim 79 is indefinite because extraembryonic tissue does not encode proteins. Also, it is unclear if the compound or library is capable of stimulating.

Claim 79 is indefinite because in step (a) it is confusing as it is written where biological activity consists of at least one of the listed activities. This rejection could be obviated by using a phrase such as, "for at least one biological activity selected from the group consisting of hematopoietic activity,...".

Claim 79 recites the limitation "the compound" in section (b). There is insufficient antecedent basis for this limitation in the claim. Section (a) refers only to compounds (plural). While the preamble may be used to breath life and meaning into a claim, it cannot be used for antecedent basis.

Claim 81 is indefinite because a functional assay cannot be a cell type. It is not clear what "cultured mammalian epiblast assays" are. If it is intended that the functional assay uses the listed types of cells, then this rejection could be obviated by using phrasing such as " wherein the functional assay utilizes a cell selected from..." in conjunction with deletion of the term " assays" at the end of the claim.

Claim Rejections - 35 USC § 112

Claims 57, 60-81 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons set forth as set forth in the previous Office action (paper #14, pages 5-7) and as restated below.

The instant specification describes three hedgehog proteins (Ihh, Shh and Dhh) and one TGF-ß family member which is BMP-4 that can stimulate undifferentiated mesodermally-derived cell to under hematopoiesis. The specification describes no compounds that stimulate the cells to undergo vascular growth, with the exception of description of vascular proliferation

(*i.e.*, endothelial cell proliferation and differentiation) by visceral endoderm (*e.g.*, p. 39, first paragraph), which is not a compound but a type of tissue. It is noted that expression of an endothelial marker (*e.g.*, *flk-1*) does not indicate that vascular growth has been stimulated. Vascular growth is a further differentiation of endothelial cells for which the markers do not provide evidence. However, the claims are directed to or encompass a diverse array of compounds, which may or may not be proteins, that have the recited hematopoietic or vascular growth property. Any compound that is a gene product expressed in an embryo's extraembryonic tissue and has one of the properties encompassed in claim 76. None of the undisclosed compounds meets the written description provision of 35 USC 112, first paragraph. Disclosure of assays or systems one could use to identify compounds in addition to the ones disclosed is an invitation to experiment without a reasonable expectation of success and does not support written description for the undisclosed compounds.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.* (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the specific proteins referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed compounds, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only naturally occurring hedgehog proteins and BMP-4, but not the full breadth of the claim meet the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claim 76 is drawn to contacting cells with an extraembyronic tissue-derived compound. Applicants point to page 34, lines 17-21 of the specification for support of such contact. The application at that section describes the requirement of contact with visceral endoderm or a compound therefrom, but does not provide support for the broader extraembyronic tissue-derived compound.

The claims are drawn to a method using a compound. There are a great multitude of compounds in extraembryonic tissue. Which specific compound(s) is the active one(s) is not stated in the claims. As stated in the previous rejection, 3 hedgehog compounds and BMP-4 have been shown to function in the claimed method. There is not description of other specific compounds. If the claim were drawn to a method of using, say extraembryonic tissue, then such a method would be described because the specification describes explant cultures in which an extraembryonic tissue mass is shown to stimulate hematopoiesis in undifferentiated mesoderm. The claims are not that broad, however, and require a compound (a narrow term compared to the term "tissue"). Therefore, the specification does not support description for the breadth of compounds.

The specification shows only that visceral endoderm (p. 39) can lead to expression of endothelial cell markers such as Flk-1 and Vezf-1. It does not describe any specific compound that does that. Therefore, the specification fails to provide an adequate written description for the broadly claimed method.

While it is true that claims drawn to methods do not necessary need the same narrowness as claims drawn to specific compounds of a class of compounds, under 35 USC 112, first paragraph, one must still be able to envision the class of compounds based on the written description of the specification. With the exception of hedgehog and BMP compounds, there is no description of compounds which induce hematopoiesis as required by the method and no specific compounds that stimulate endothelial proliferation or differentiation. It does not appear

that Applicant was in possession of compounds other than those just mentioned that could be used in the claimed method.

Claims 57 and 60-81 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention for the reasons set forth in the previous Office action (paper #14, pages 7-8) and as restated here.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The invention is drawn to a method of stimulating a population of undifferentiated mesodermally-derived cells (*e.g.*, hematopoietic stem cells, yolk sac mesoderm) to undergo hematopoiesis, endothelial cell differentiation or endothelial cell proliferation by a compound contacting the cells. The compound must be a "hedgehog or WNT" according to claim 57 or "an embryo's extraembryonic tissue derived compound" according to claim 76. There is no showing of a WNT compound in the instant application or prior art that is both derived from extraembryonic tissue and able to stimulation at least one of hematopoiesis, endothelial cell proliferation and differentiation in undifferentiated mesodermal cells. Additionally, it has been shown in the prior art that there are many WNTs and they do not all have the same activity, so which WNT would function in this method is not disclosed or known. Therefore, the claimed method using WNT is not enabled.

The prior art teaches that BMP-4 and to a lesser extent BMP-2 when introduced into *Xenopus* oocytes cause formation of blood cells (Hemmati-Brivanlou et al., U, Dev. Genet., 1995, see below). Dickson et al. (AX, Dev., 1995) showed that TGF-ß1 is necessary for both proper vasculogenesis and hematopoiesis, particularly in differentiation of yolk sac mesoderm.

Even though a common molecule can *influence* both vasculogenesis (for which endothelial cells are necessary) and hematopoiesis, these are distinct events affecting distinct cell types. Other molecules, such as VEGF are active in vasculogenesis but not hematopoiesis (*e.g.*, Carmeliet et al., AO, Nature, 1996, and Moses, DJ, Int. Re. Cytol., 1995). Also taught in the prior art is the native receptor of hedgehog called patched (ptc, *e.g.*, Goodrich et al., BW, Genes Dev., 1996). It is acknowledged that relative skill of those in the art relating to what tissues give rise to hematopoiesis and what markers are indicative of hematopoiesis is high; however, the skill of those in the art is not high concerning which compounds induce or might induce hematopoiesis. While there are suggestions in the art of compounds which might induce hematopoiesis, the predictability about whether or not those compounds actually can is low. For example, it has been shown that mice embryos deficient in the flk-1 receptor (*i.e.*, a receptor for VEGF) have severely reduced hematopoiesis and vasculogenesis (Shalaby et al., EI, Nature, 1995). Nevertheless, it has not been shown that VEGF itself can induce hematopoiesis, although it has clearly been shown to induce vasculogenesis. For vascular growth it was known that presumptive endothelial cells give rise to blood vessels; however, the markers for endothelial cells alone will not distinguish those cells which will specifically form blood vessels (*e.g.*, flk-1). It does not appear that at the time the invention was made there were definitive markers for vascular endothelial cells. While prior art compounds were shown to induce vascular growth, the predictability about whether a compound not previously known to have that function could induce vascular growth of undifferentiated mesodermally-derived cells was low.

The instant application has no working examples of stimulating undifferentiated mesodermally-derived cells to undergo vascular growth. Nor are there examples of any compounds other than Shh, Ihh or BMP-4 stimulating the cells to undergo hematopoiesis. However, results from studies listed in the specification (page 20-21) using Ihh and Dhh knockout transgenic mice would lead the skilled artisan to reasonably expect that Dhh could also be used in the claimed method. There are no examples in the specification or prior art of a hedgehog protein binding to and activating any receptor other than ptc. There is no evidence in the prior art or instant specification that a Drosophila hedgehog polypeptide can activate a vertebrate patched receptor or *vice versa*.

The claims as written have great breadth in terms of stimulation of hematopoiesis, endothelial differentiation or endothelial proliferation. It is noted that expression of an endothelial marker does not indicate that endothelial proliferation has been stimulated. On the other hand, the breadth of the claims added by the types of cells that may be undifferentiated mesodermally-derived cells is *not* great since the developmental lineage of such cells has been well known in the art and the specification provides guidance and examples of the types of cells that can be successfully used in the claimed method. Nevertheless, breadth is added by what the compound can be. In claim 76, the only limitation attached to the compound is that it be "an embryo's extraembryonic tissue derived compound". It is noted that in the specification, a "hedgehog compound" (claim 57) is defined as a hedgehog protein or analog or derivative thereof or agonists or antagonists of hedgehog protein receptors of functional equivalents of any of these. Therefore, such a compound need not have any resemblance to a naturally occurring Ihh, Dhh or Shh polypeptide. In terms of the compounds that can be used, including the derivatives and analogs, the claims are single means claims (see MPEP 2164.08), i.e., where a means recitation does not appear in combination with another recited element of means, is subject to an undue breadth rejection under 35 U.S.C. 112, first paragraph. In re Hyatt, 708 F.2d 712, 218 USPQ 195 (Fed. Cir. 1983) (A single means claim which covered every conceivable means for achieving the stated purpose was held nonenabling for the scope of the claim because the specification disclosed at most only those means known to the inventor.). When claims depend on a recited property, a fact situation comparable to Hyatt is possible, where the claim covers every conceivable structure (means) for achieving the stated property (result) while the specification discloses at most only those known to the inventor. Further, defining a polypeptide by its activity is analogous to the situation argued for DNA defined by the activity of the polypeptide it encodes as put forth in *Ex parte Maizel* (27 USPQ2d 1662 at 1665):

> Appellants have not chosen to claim the DNA by what it is but, rather, by what it does, i.e., encoding either a protein exhibiting certain characteristics, *or* a biologically functional equivalent thereof. Appellants' claims might be analogized to a single means claim of the type disparaged by the Court of Customs and Patent Appeals in *In re Hyatt*, 708F.2d 712, 218 USPQ 195 (Fed. Cir. 1983). The problem with the phrase "biologically functional equivalent thereof" is that it cover any conceivable means, i.e., cell or DNA, which achieves the stated biological result while the specification discloses at most, only the

> specific DNA segment known to the inventor. Clearly the disclosure is not commensurate in scope with the claim."

In the current case, the compound is being defined by what functional property it has, not by what it is. Disclosure of assays or systems (*e.g.*, transgenic mice) one *could* use to identify compounds is an invitation to experiment without a reasonable expectation of success and does not support enablement for the scope of undisclosed compounds.

For claim 75 and dependent claims, the first compound must be capable of acting synergistically with a second compound. The specification on page 11, line 20, defines a "Synergist effect" as "for two or more compounds where little or no biological effect is observed with the compounds alone but together the compounds have a potent biological effect." There is no teaching in the specification or the prior art of such compounds capable of having one of the required effects together where each compound alone as little or not effect.

For these reasons, it would require undue experimentation to practice the invention commensurate in scope with the broad claims.

The instant specification provides an invitation to experiment without a reasonable expectation of success. It is not disclosed in the specification or prior art what compounds besides Ihh, Shh, Dhh and BMP-4 and-2 would be reasonably expected to be derived from extraembryonic tissue and stimulate at least one of hematopoiesis, endothelial proliferation and differentiation. By requiring a "compound", the claims have a narrower breadth than if "visceral endoderm" was required. Because of the vast number of compounds within extraembryonic tissue and the unknown physical characteristics and biological activities of those compounds as related to the current invention, it would require not routine but undue experimentation to practice the invention commensurate in scope with the claims.

The predictability of specific compounds is low, with the exception of those few shown in the specification to have the required property. "Visceral endoderm" has been shown to induce hematopoiesis, but which of the mass of compounds derivable from visceral endoderm has that property is not disclosed. Providing methods of testing for the activity are an invitation to experiment without a reasonable expectation of success. Protein purification is not trivial, and identifying individual compounds from a tissue which have a specific function would require undue experimentation in part because which of individual compounds would be reasonable

expected to have the required property is unpredictable outside the family of compounds which are hedgehog or bone morphogenic proteins.

Claim Rejections - 35 USC § 102

Claims 57,62-64, 69 and 76 are rejected under 35 U.S.C. 102(b) as being anticipated by Zeigler et al. (V, Blood, 1994) for the reasons set forth in the previous Office Action (paper #14) on page 8 and as repeated here.

Zeigler et al. teach stimulating a population of undifferentiated mesodermally-derived cells (hematopoietic stem cells including fetal liver cells) to undergo hematopoiesis by applying TPO to the cells (p. 4049, col. 1). TPO is a secreted protein and was effective when added to the culture medium (middle of second paragraph on p. 4049).

Note: Thrombopoiesis is the process of platelet production which is part of hematopoiesis. Hematopoiesis is a broad term describing many processes such as thrombopoiesis, red blood cell production and white blood cell production. Therefore, stimulation of thrombopoiesis is stimulation of hematopoiesis.

Conclusion

This is a CPA of applicant's earlier Application No. 09/021,660. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however,

event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (703) 305-5791. Dr. Kaufman can generally be reached Monday through Thursday from 8:30AM to 12:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (703) 308-6564.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

Claire M. Kaufman, Ph.D.

Patent Examiner, Art Unit 1646

December 27, 2000